CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DIETHATYL ETHYL

Chemical Code #1995, Tolerance #00402
SB 950-047

November 26, 1986
Revised 7/6/87, 6/3/88, 9/21/89, 7/13/90, 11/18/91, 11/29/93

I. DATA GAP STATUS

Combined rat: (Chronic + onco)	No data gap, no adverse effect.
Chronic dog:	No Data gap, no adverse effect.
Onco mouse:	No data gap, no adverse effect.
Repro rat:	Data gap, inadequate study, no adverse effect indicated.
Terato rat:	No data gap, no adverse effect.
Terato rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotox:	Not required at this time.

---**

indicates acceptable study
Bold face indicates possible adverse effect
File name: T931129
Revised by G. Chernoff, 7/13/91; M. Silva, 11/18/91; M. Silva, 11/29/93.

Rectified through volume #: 055, record #: 118596

NOTE: The following 1-liners are general summaries only. For more complete study reviews, see the respective worksheets.

II. TOXICOLOGY SUMMARY

COMBINED RAT (CHRONIC + ONCO)

**034-036 036985-7, "Two-year Chronic Oral Toxicity Study with Antor (Technical) in Albino Rats", (IBT #8560-10525 [valid study] 1/15/81). Diethatyl ethyl (89-93%, 3 lots); fed at 0, 200, 1,000 or 5,000 ppm in diet, 2 years, to 50/sex/group; no adverse effect is reported; marginal liver findings in males and bile duct hyperplasia in females at high dose; COMPLETE, ACCEPTABLE (JR(G), 2/14/86).

EPA 1-liner: Minimum. Oncogenic NOEL > 5000 ppm; systemic NOEL = 200 ppm (liver vacuolization); IBT - valid.

COMMENT: Although this is a valid study according to the list compiled by EPA and all of the data are presented needed for an acceptable report, the study was conducted by IBT, a laboratory known to have produced "invalid" reports.

031 014968, "Two Year Chronic Oral Toxicity Study with Antor (Technical) in Albino Rats: Grading of Histopathological Lesions", (FBC limited, Chesterfield Research Station, study no. 83407, FBC audit of IBT study #8560-10525, record no. 036985-7, 6/6/83. Report on histological and non-neoplastic lesions graded (JR(G), 3/25/85 & JSK, 6/3/88).

012 976544, Progress summary (2 paragraphs) of #36985-7.

018 038460, First 15 pages (p.1-15) of IBT #8560-10525, full report in #036985-7.

024 976509, Pages 1-77 identical to #036985-7.

024 021615, Supplementary histopathology report for #036985-7

007 009321, "Two Year Chronic Oral Toxicity Study - Albino Rats, Antor Technical", (IBT, study no. IBT #8560-08350, 10/9/76). Reported treatment-related renal changes were focal and consisted of the presence of proteinaceous like filtrate and casts. Severity of lesions reported to be severe to mild. Invalid IBT study. (JR(G), 3/25/85 & JSK, 6/3/88).

EPA 1-liner: No CORE grade. Seven-month preliminary report. NOEL = 200 ppm, LEL = 5000 ppm (Tubular resorption droplets in kidneys).

012 976545, Three-paragraph summary of interim sacrifice histological findings in #009321 (invalid IBT study).

012 038458, Four-paragraph summary of #009321 (invalid IBT study).

CHRONIC TOXICITY, DOG

** 044 060187 To 060190, "Technical Diethatyl-Ethyl: 104 Week Dietary Toxicity Study in Dogs", (Huntingdon Research Centre, Huntingdon, England, study no. Tox. 83098, 9/2/86). Diethatyl-Ethyl, purity 94.3%-96.7%, in feed at 1250, 250, 50, 10, or 0 ppm to 6 Beagles/sex/group. **Effects:** blood pressure increased form week 24, in males at 1250 ppm and sometimes at 250 ppm. NOEL = 50

ppm, based on increased red cell turn over (increased erythroid cells with corresponding reduction in myeloid:erythroid ratio) and increased liver weights at 250 and 1250 ppm (in females at 1250 ppm, approximately 20%). ACCEPTABLE. (Gee, 6/3/88).

045 060188, Supplement to 060187: Residues of diethatyl ethyl in dog plasma.

045 060189, Supplement to 060187: T67B-Determination of diethatyl ethyl concentrations.

045 060190, Supplement to 060187: Immunological investigations of sera from dogs.

045 060273, Supplement to 060187: Toxicological significance of the positive Coombs test.

045 060274, Supplement to 060187: Toxicological significance of haematological findings.

031 014967, "Diethatyl Ethyl: Investigations of Mechanism of Positive Antiglobulin Reactions Associated with Prolonged Dietary Administration to Dogs", (FBC Limited, Huntingdon Research Centre, study no. Tox/83106, September 1983). Diethatyl ethyl (technical grade), purity not stated, fed at 0, 200, 1000 or 5000 ppm to 4 Beagles/sex/group for 26 weeks. Reported treatment-related pattern of red cell effect was shown to be characterized by a concurrent positive direct antiglobulin reaction. (JR(Gee), 3/25/85 & JSK, 6/3/88).

031 014966, "Technical Diethatyl Ethyl: Oral Toxicity Study in Dogs (Final Report: Repeated Dietary Administration for 27 Weeks)", (Huntingdon Research Centre, study no. Tox 82082, March 1984). Diethatyl ethyl, purity not stated (technical), fed at 0, 200, 1000 or 5000 ppm to 6/sex/group. This study was set up as a 1 year study but curtailed because of toxicity. Report does not contain appendicies. Notation in front of volume 031 indicates a chronic dog study is in progress for completion in August 1986. (J.R. Gee), 3/25/85 & JSK, 6/3/88).

ONCOGENICITY, MOUSE

**037 036988, "Twenty-four Month Chronic Oral Oncogenicity Study with Antor (Technical) in Swiss White Mice", (IBT #8580-08351 [valid]), 6/9/81). Diethatyl ethyl (technical 93.6 and 89.4%) given at 0, 200, 1,000 and 5,000 ppm in the diet to 50/sex/group; no onco effects noted, decreased wt. gain in high dose. Oncogenicity NOEL > 5000 ppm; ACCEPTABLE. (JR(G), 2/18/86).

EPA 1-liner: Minimum. Oncogenic NOEL > 5000 ppm (HDT); histologic NOEL > 5000 ppm; significant decrease in body weight gain at 5000 ppm in both sexes.

023 021614, Addendum to # 036988 - Histological findings.

012 976549, Supplemental to 036988; Summary of progress for IBT #8580-08351.

018 038461, Supplemental to 036988; Pages 1-6 of IBT #8580-08351.

023 976493, Expanded summary, see #036988 above for review. Reviewed by JR(G), 3/22/85. Note: printout shows no record #976493. Volume 23 has only the record # 21614. There is a worksheet that has been assigned the number 976493.

REPRODUCTION, RAT

055 118596, "Diethatyl-Ethyl (Antor), Rat Two-Generation Reproductive Toxicity Study", (Irvine, L.F.H., Toxicol Laboratories Limited, England, Report # SHC/8/R, 2 October 1992).

Diethatyl-ethyl technical (purity not stated) was administered in the diet to Sprague-Dawley (OFA-SD (IOPS-Caw), 25 or 28/sex/dose) at 0 (Rodent Diet), 100, 1000, and 10000 ppm. F0 treatment began 10-weeks prior to mating. Reproduction NOEL > 10000 ppm (There were no adverse reproductive effects observed at any dose in F0 or F1 generations). Systemic NOEL = 100 ppm (Both sexes showed reduced body weights at 10000 ppm (F0) or ≥ 100 ppm (F1 males) and 10000 ppm (F1 females). Food consumption was significantly decreased in females (F0 at ≥ 100 ppm & F1 at ≥ 1000 ppm) during gestation and (F0 at 10000 ppm & F1 at 10000 ppm) during lactation. Mean and/or relative liver weights were increased and pituitary, testes and ovary weights were significantly decreased in both generations at primarily ≥ 1000 ppm (although female F0 pituitary absolute weights were significantly decreased at ≥ 100 ppm). Developmental NOEL = 1000 ppm (Reduced F1 and F2 litter size and delayed pup development at 10000 ppm). **Adverse reproductive effects were not observed**. **Unacceptable**, but possibly upgradeable upon submission of diethatyl-ethyl purity and chemical characteristics plus data for the stability, homogeneity and concentration of the compound in diet (sampled during the study). Green & Silva, 8/31/93.

012 976554, Summary (4 page) of progress in an IBT study (JR(G), 9/5/85).

025 021616, "Three-generation Reproduction Study in Rats with Antor (Technical)", (Hazleton [revised final report - 122 pp.], 2/20/81). Diethatyl ethyl, 93.3%, was fed to groups of 8 males and 16 females at dose levels of 0, 200 and 2000 ppm in the diet for 3 generations, 2 litters/generation. No adverse reproductive effects were reported at either of the dose levels tested; NOEL > 2000 ppm. The study was originally reviewed as unacceptable by J. Gee, 3/26/85 (no MTD, no dose justification, only 2 doses tested). Submission of supplemental information (CDFA Record Nos. 067005, 067468, 067469, and the letter dated 2/23/90 in Vol. 050) failed to justify the dose selection, or provide evidence of an MTD. The study remains **UNACCEPTABLE**, and is no longer considered upgradeable (G. Chernoff, 7/13/90).
EPA 1-liner: Minimum. Reproductive NOEL > 2000 ppm (HDT); maternal NOEL = 200 ppm (higher liver/body weight ratio in female P_3 and male P_2; mean higher testes weight; fetotoxic NOEL = 200 ppm (lowered pup weights.)

018 038462, Supplement to 021616; duplicate of pgs. 1-17.

038 036989, Supplement to #021616; expanded report (177 pp.) including additional individual postnatal litter data. (JR(G), 2/18/86).

050 (no number), Supplement to 021616; a letter from P.F. Paul, dated February 23, 1990, presenting an argument for dose level justification, reviewed in worksheet 021616.S01 (G. Chernoff, 7/13/90).

047 067469, "Two-Week Pilot Study with Hercules 22234 Technical in Albino Rats", (Industrial Bio-Test Laboratories, IBT # 622-02900, 2/26/73). Hercules 22234 Technical (Diethatyl-Ethyl) administered at concentrations of 0 (corn oil), 500, 1000, 2000, 5000, 10000 or 30000 ppm in the diet of 5 rats/sex/group for 2 weeks. **No adverse effect.** NOEL ≥ 5000 ppm (reduced body weight and food consumption). This study is supplementary to 021616 (Kishiyama & Silva, 9/12/89).

047 067005, "Ninety-Day Subacute Oral Toxicity Study with Hercules 22234 Technical in Albino Rats", (Industrial Bio-Test Laboratories. IBT no. 622- 03059, 8/30/73). Supplemental to 021616. No worksheet: **invalid study**. (Kishiyama & Silva, 9/12/89).

047 067468, "Ninety-Day Subacute Oral Toxicity Study in Albino Rats, Antor Technical-Histopathological Re-examination", (Industrial Bio-Test Laboratories, IBT #B 3059, 10/9/76). Addendum to an invalid study (no worksheet). Supplemental to 021616 (Kishiyama &

Silva, 9/12/89).

047 067470, "Kidney Slide Review from Antor Technical 90-Day Rat and Antor Metabolite 90-Day Rat", (Industrial Bio-Test Laboratories, University of Maryland; IBT #B 8166 and B 3059, 10/11/76). Diethatyl-Ethyl was administered in the diet of male rats at concentrations of 0, 500, 1000, 2000 or 5000 ppm for study B 3059 and B 8166 (no 500 ppm group). An assessment of kidney lesions was made from a review of slides from these studies. Kidney alterations in both studies were minimal and sublethal with no evidence of preneoplastic lesions. These data are supplementary to study 021616, however, since they are from an invalid IBT study, they cannot reasonably be used to justify dose (Kishiyama & Silva, 9/12/89).

TERATOLOGY, RAT

012 976553, "Teratology Study in Rats, Antor," (Litton Bionetic, Kensington, MD, Project 20942, 9/78). Diethatyl-ethyl (Antor technical, 94%) dosed by oral gavage to groups of 18-19 pregnant CRL:COBS CD(SD)BR rats days 6-15 of gestation; 0, 100, 250 or 500 mg/kg; No maternal toxicity observed, no teratogenic or fetotoxic effect observed; NOEL for maternal and fetal effects are greater than 500 mg/kg; UNACCEPTABLE, Not upgradeable (dose level not adequately justified with no evidence of MTD, missing dosing solution analysis) (N. Hughett 6/25/87, J. Gee 3/22/85 & 7/3/87.

EPA 1-liner: Minimum. Teratogenic LEL > 500 mg/kg (HDT); fetotoxic NOEL = 250 mg/kg (increased incidence of subcutaneous hematomas)

021 976550, Incomplete report of 976553. UNACCEPTABLE (insufficient information for assessment). (JR(G), 3/22/85).

041 051360, Rebuttal and supplemental data to 976553 - individual maternal body weight and food consumption. (JG, 7/3/87).

** 050-051, 053-054 087171, 095624, 098420, 112780 "Technical Diethatyl-ethyl (CR 20219/3): Rat Teratogenicity Study, (P.W. Harvey, Schering Agrochemicals Ltd., Study No. TOX 89202, 1/18/90). Diethatyl-ethyl, 94.6%, batch CR 20219/3, was administered by oral gavage to mated female rats (30/dose) at 0 (1% methyl cellulose vehicle control), 125, 500, or 2000 mg/kg/day on gestational days 6-15. Maternal NOEL = 125 mg/kg/day (reduced weight gain at 2000 mg/kg/day; urogenital and facial soiling at $\underline{\geq}$ 500 mg/kg/day). Developmental NOEL = 125 mg/kg/day (Fetal weights were reduced at 2000 mg/kg/day and there was an indication of increased resorptions at doses of $\underline{\geq}$ 500 mg/kg/day. Multiple congenital contractures were significantly elevated at 125 mg/kg/day, but not at the higher doses--may not be treatment reelated.) Previously reviewed (Chernoff, 7/13/90 & Silva, 11/6/91) as **UNACCEPTABLE** but possibly upgradeable, upon submission of the requested information (054 112780), the study is **ACCEPTABLE**, with no adverse effects. M. Silva, 11/6/91.

054 112780 This rebuttal volume provided supplementary data to support study 050 087171. No worksheet. M. Silva, 11/24/93.

050 086124, "Determination of Diethatyl-Ethyl Concentrations in Methyl Cellulose Suspensions for a Preliminary Dose Range Finding Study and a Teratology Study in the Rat", (J.H.M. Bright, Schering Agrochemicals, Report RESID/89/68, 2/19/90). Supplemental to CDFA Record No. 087171; no worksheet provided (G. Chernoff, 7/13/90).

TERATOLOGY, RABBIT

022 021613, "Antor Teratology Study in Rabbits", (IRDC #79-01). Expanded summary report of 19 pp., 12/21/79). Antor (diethatyl ethyl, technical), to 16/group at 0, 100, 250 or 500 mg/kg by oral gavage, days 6-18; high dose resulted in 7/16 deaths, 6 from unknown causes; vessel variations observed in all dose levels, skeletal variations in the 2 high doses. Apparent NOEL is 250 mg/kg. **UNACCEPTABLE** - missing individual data and inadequate number of litters even at mid-dose (JR(G), 3/22/85).

EPA 1-liner: Supplementary. The teratogenicity and fetotoxicity could not be evaluated due to inadequate number of pregnant dams at 500 and 250 mg/kg/day; maternal NOEL = 250 mg/kg/day (decreased body weight gain)

038 036991, Supplement to 021613; 3 appendices. Review by JR(G), 2/20/86.

012 038459, Supplement to 021613; 2 pg. progress report.

018 976552, Supplement to 021613; pages 1-9.

**031 014965, "Effect of Diethatyl Ethyl on Pregnancy of New Zealand White Rabbit", (Huntingdon, 27 pp., 11/9/82). Diethatyl ethyl, 94-95%, 16/group given 0, 100, 250 or 500 mg/kg by oral intubation, days 6-18 of gestation; NOEL (maternal) = 250 mg/kg (body weight), Developmental NOEL $\geq$ 500 mg/kg/day. ACCEPTABLE (with data from #36992 and #43869) NO ADVERSE EFFECT Replaces 21613. (JR(G), 3/25/85, 2/20/86 and JG and JAP, 9/22/86).

EPA 1-liner: Minimum. Teratogenic NOEL > 500 mg/kg (HDT); fetotoxic NOEL >500 mg/kg; maternal NOEL = 100 mg/kg (reduced body weight).

038 036992, Supplement to #014965; 77 pp. report, with appendices. More complete version of 014965 (JG and JAP, 9/22/86).

039 043869, Addendum to 014965; analyses of dosing solutions.

GENE MUTATION

007 009312, "Salmonella", (5/6/75, Litton Bionetics, #2526). Strains TA1535, TA1537 and TA1538, duplicate plates at 100 ug/plate. UNACCEPTABLE (strains, concentration, no repeat). No adverse effect noted. Activation with mouse, rat or monkey homogenates (JR(G), 3/25/85).

027 003010, Summary of data from #009312.

**045 060275, "Technical Diethatyl Ethyl: Ames Bacterial Mutagenicity Test." (Huntingdon Research Centre, UK, 2/20/87). Diethatyl ethyl, technical, lot CR 20219/3, 94.6%; tested with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 at 0 (solvent - ethanol and no solvent), 50, 150, 500, 1500 and 5000 µg/plate, triplicate plates, two trials, with and without rat liver activation; slight cytotoxicity with TA100 at 5000 µg/plate; no evidence for increase in revertants. ACCEPTABLE (Gee, 6/1/88).

CHROMOSOME EFFECTS

012 976557, "Evaluation of: Antor X21591-3, Mouse Micronucleus Bioassay", (Booz, Allen and Hamilton, Florham Park, N. J., 12/8/78). Diethatyl ethyl, technical, X21591-3, fed at 0, 500, 2000 or 5000 ppm to 5 Swiss-Webster ICR mice/sex/group for 5 days, sacrificed on 6th; slight dose-related decreased b.w. gain; micronucleated RBC ~ same for all doses. TEM as positive

control. UNACCEPTABLE (single sampling time, no individual data/animal). (JR(G), 9/5/85). EPA 1-liner: Minimum. NOEL => 5000 ppm (HDT).

038 036990, Identical to #976557 with addition of 2 appendices, a journal article on the methodology of a micronucleus assay, and the experimental protocol for this study.

045 060276, "Technical Diethatyl Ethyl: Metaphase Chromosome Analysis of Human Lymphocytes Cultured in vitro," (Huntingdon Research Centre, UK, 5/12/87). Diethatyl ethyl technical (CR 20219/3, 94.6%) was tested for chromosome aberrations with pooled human lymphocytes from 5 healthy male donors (aged 20-35). Cells were separated on a gradient. Concentrations were (2 cultures/concentration): 0 (ethanol solvent), 6, 30, or 60 µg/ml (no activation) or 0 (ethanol solvent), 25, 125 or 250 µg/ml; 250 µg/ml (limit of solubility--with S-9 from rat liver). Cells were in culture with phytohemagglutinin for 48 hours, then exposed to the test article 22 hours (no activation) or 2 hours (with activation), followed by an additional 20 hours. Harvest was 70 hours after initiation of cultures; colchicine to collect metaphases (5 slides per concentration, scored 100 cells/culture). There was no evidence of an increase in aberrations with treatment; mitotic index decreased at 30 and 60 mg/ml compared with controls. The study was previously reviewed as unacceptable (Gee, 6/2/88), upon receipt of information on source of human lymphocytes, number of subjects, justification for a single harvest time, the study has been upgraded to **acceptable (Kishiyama & Silva, 9/13/89).

DNA DAMAGE

007 038457, "Saccharomyces cerevisiae", (5/6/75, Litton Bionetics #2526). Strain D4 tested at 100 ug/plate with mouse, rat and monkey liver activation. No details with a single plate and value. No evidence of toxicity or justification of concentration. UNACCEPTABLE. (JR(G), 3/25/85.).

**033 035988, "Technical diethatyl ethyl: Unscheduled DNA Repair Synthesis in Cultured Mammalian Cells", (Huntingdon, 9/30/85). Diethatyl ethyl, technical, 95.4%, HeLa S3 cells were exposed for 3 hours + rat liver activation from 0 to 1024 ug/ml, 12 conc, duplicate cover slips, 2 trials, cytotoxic at 2-3 highest conc., no evidence of UDS in grains/100 nuclei. Initially reviewed as unacceptable based on the number of cultures (4) per concentration. Reconsideration found this a minor variation and the study was upgraded. COMPLETE, ACCEPTABLE (AA, 11/13/85 and JG and JAP, 6/16/86).

NEUROTOXICITY

Not required at this time.